1,158,283

PATENT SPECIFICATION 1,158,283

DRAWINGS ATTACHED.

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COMPLETE SPECIFICATION.

Composition to be Applied to Skin and Process for Preparing Same.

We, FOSTER-MILBURN COMPANY, a corporation organized under the laws of the State of New York, United States of America, of 468, Dewitt Street, Buffalo 13, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compositions to be applied to the skin of humans and domestic animals and having increased percutaneous absorption through and retention in the skin and a process for producing such compositions.

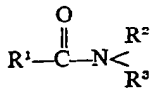
More particularly, this invention is directed to a preparation for increasing the percutaneous absorption and cutaneous retention in the stratum corneum of stable, topically active, chemical compounds and a process for preparing the same.

The epithelial layer of human skin, also referred to as the epidermis, protects the more delicate underlying portions of the human body from chemical irritation, bacterial attack and other various harmful external conditions. The outer or surface division of the epidermis, called the stratum corneum or horny layer, acts as the barrier to penetration of external substances into the body. While it is essential to human health that this relatively impermeable barrier be maintained as such, instances arise where an increase in skin penetration by a selected chemical compound is highly desirable, as for example in the treatment of subcutaneous inflammation.

Various methods for increasing the permeability of the skin have been disclosed. Increased penetration of the epidermis has been achieved by occlusion of the skin with metal guards or plastic wraps. Temperature increases have enchanced the absorption of oxygen and methyl salicylate. Increases in skin temperature and the relative humidity of the adjacent atmosphere have resulted in increased penetration of water vapor and other substances through the skin. Hydration of the skin through water soaking, for example, has resulted in as much as a twelve fold increase in penetration.

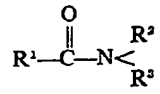
While it is not known why the stratum corneum or horny layer acts as such an effective barrier it could be said as a general rule, until now, that the vehicle in which a given chemical compound was dissolved or solubilized in had little or no effect on the skin penetration rate of the compound.

In accordance with the invention there is provided a process for producing a composition to be applied to the skin and having increased percutaneous absorption through and retention in skin as hereinafter defined which comprises solubilizing a stable, topically active beneficial chemical compound as hereinafter defined in a pharmaceutically acceptable vehicle having as one component an amide having the structural formula:



wherein R^1 is a hydrogen or methyl radical, R^2 is a hydrogen or alkyl radical containing not more than 2 carbon atoms; and R^3 is an alkyl radical containing not more than 2 carbon atoms.

The invention further provides a composition to be applied to the skin and having increased percutaneous absorption through and retention in skin comprising a stable, topically active chemical compound which is an anti-acne agent, an anti-inflammatory agent, an anti-cholineric, an emollient, a sex hormone, a crude tar, an anti-psoriatic agent or an anti-metabolite, solubilized in a pharmaceutically acceptable vehicle having as one component an amide having the structural formula:



wherein R^1 is a hydrogen or methyl radical, R^2 is a hydrogen or alkyl radical containing not more than 2 carbon atoms; and R^3 is an alkyl radical containing not more than 2 carbon atoms.

Illustrative of the amides which may be utilized in the process of this invention are N,N-dimethyl formamide, N-methyl formamide, N,N-diethyl acetamide, N-ethyl formamide, N-ethyl acetamide, N,N-diethyl acetamide, N,N-dimethyl acetamide and N-methyl acetamide. The preferred amides are N,N-dimethyl formamide, (DMF), N,N-dimethyl acetamide (DMA) and N,N-diethyl acetamide (DEA). The most preferred amide is N,N-dimethyl acetamide.

Preferably 0.001% by weight to 80% by weight of the topically active chemical compound is solubilized in from 99.999% by weight to 20% by weight of a pharmaceutically acceptable vehicle. The pharmaceutically acceptable vehicle may comprise the amide alone but will preferably contain 25% to 95% amide. The skin is contacted with the composition for about 15 seconds.

The accompanying drawing is presented to facilitate an understanding of the invention. The drawing is a diagrammatic illustration of a cross sectional view of the anatomy of epidermis, highly magnified. The stratum corneum (A) is the outer division of the epidermis composed of dead epithelial cells and referred to generally hereinafter as the horny layer. All the barrier properties of the skin, i.e., resistance to penetration, exist in the cellular layer identified as A in the drawing.

Once a chemical substance passes through the horny layer of the epidermis absorption or penetration through the remaining stratum granulosum (B), stratum malpighii (C) and stratum germinativum (D) on into the first connective tissue beneath the epidermis, the dermis, and remainder of the body is practically quantitative. Below the cellular layer identified as A there is very little resistance to penetration or absorption. Thus the term percutaneous absorption means that a substance passes from the top of the skin through the horny layer of the epidermis, area A of the drawing, into the cellular epidermis and from there into the corium or dermis. Once the substance has penetrated through the horny layer this then constitutes percutaneous absorption for the purposes of this invention. The passage of the substance on into the corium and into the systemic circulation is considered to be the effect or continuing result of percutaneous absorption. Absorption into the horny layer alone with no immediate further absorption or penetration deeper into the epidermis is not considered to be percutaneous absorption but is referred to rather as retention.

The term retention, then, refers to absorption of substances into the horny layer alone without further continuous passage into the layers identified as B, C, D and beyond. Thus the horny layer presents a depot or reservoir for a topically applied substance. It should be understood, of course, that over a period of time, there may be a slow rate of absorption of the substance originally retained in the horny layer so that neither the concept of percutaneous absorption nor retention and reservoir build up is absolute but are interrelated relative terms used to describe the process of skin penetration.

In nature when a penetratable substance is applied to the skin, an extremely small percentage of the substance is absorbed into the horny layer and retained there. An even smaller percentage of the substance absorbed into the horny layer passes through the horny layer into the layers identified as B, C and D and thence on into the systemic circulation of the human. Thus, there is both natural retention and percutaneous absorption.

The invention provides for a surprising increase in the rate of percutaneous absorption and retention and in the amount of penetratable substance actually absorbed.

The substances referred to herein as stable, topically active chemical compounds are beneficial chemical substances which can be applied topically to the skin for the purpose of medicating surface or subsurface diseases or systemic disturbances or creat-

ing skin conditions helpful in alleviating harmful or annoying external factors.

These topically active chemical compounds are stable when solubilized in the class of amides set forth above. This does not mean that these compounds must have long periods or shelf life, when incorporated in the application medium, as is generally understood concerning stability in the pharmaceutical industry. Rather for the purposes of this specification by stability is meant that the compounds will not react readily or otherwise become unstable within the short time period necessary to solubilize the compounds in the lower alkyl amide preparations and apply the preparations to the skin.

By the term solubilized is mean that the stable topically active compounds of this invention must have the ability to be dissolved or held in suspension by normal mixing or shaking operations in the operable class of amides set forth above, to the extent of about 0.001% by weight of stable, topically active compound in the amide.

Generally speaking many chemicals are useful in treating surface and subsurface conditions by topical application and can be made more effective if both their percutaneous absorption and retention rates are increased such that greater concentrations of the chemical will penetrate through the horny layer and also be retained in the horny layer.

Antimicrobial agents, anti-acne agents, antiseborrheic agents, antipsoriatic agents, anticholinergics, anti-inflammatory agents, antimetabolites, sex hormones, emollients, derivatives, extracts and components of crude coal tar and sunscreens are examples of classes of beneficial chemical compounds which because of the manner in which they are used in topical application exhibit enhanced results or activity due to increases in the amount of substance and the rate at which the substance is percutaneously absorbed or retained.

Anti-inflammatory agents such as triamcinolone acetonide, fluocinolone acetonide, betamethasone valerate and hydrocortisone are stable, topically active compounds which exhibit the required characteristics and are rendered more effective in treating inflammatory disorders of the skin and subsurface areas of the body by increasing their percutaneous absorption and retention. The process of the invention renders these compounds five to fifteen times more penetratable and since greater amounts of the steroids are available at the inflammed areas, vasoconstriction of the blood vessels is greater with accompanying reduction in swelling and less entrance of lymph and white blood cells into the affected area.

Anticholinergic drugs when introduced into the skin are capable of inhibiting sweating. Thus they have been found effective in the control of miliaria rubra (prickly heat). Actually, ordinary topical applications of these drugs alone or in vehicles other than those utilized in the instant invention process will give certain small amount of axillary sweat inhibition which is not generally satisfactory Experimental data shows that 1-methyl-3-pyrrolidyl α-phenylcyclohexane-glycolate methobromide (otherwise known as hexopyronium bromide) was compatible with the amides utilized in this process and showed greatly increased sweat inhibition when applied in accordance therewith.

Antimetabolites which have been shown to cause clearing in psoriatic lesions and have utility in tumor therapy, for example, 5-fluorouracil, 4-amino-n^{10}-methylpteroylglutamic acid and 6-mercaptopurine have been found to be compatible with the amides of the process and show vastly increased percutaneous absorption and retention when applied to skin according to the teachings of this invention.

In clinical applications antimicrobial agents such as antiparasitic, antibacterial, antifungal, antiviral and antirickettsial agents have been shown to exhibit increased percutaneous absorption and retention when used in the present process. Erythromycin; 2,2^1-methylenebis (3,4,6-trichlorophenol); 3,4^1,5-tribromosalicylanilide; 3,4,4^1-trichlorocarbanilide; nystatin; undecylenic acid; sulfur; salicylic acid; parachlorometaxylenol; 2-(4^1-thiazolyl)-benzimidazole; iodine and iodine compounds, as iodochlorhydroxyquin, 5-iodo-2^1-deoxyuridine are some of the examples of the antimicrobial agents. They exhibit an outstanding example of the utility of this invention, particularly regarding the retention factor. When these antimicrobial agents are retained on the skin in greater concentrations, they build up a continuing, long-lasting resistance to microbes and keep the microbial population at minimal levels so as to speed healing and prevent renewed infection or attack.

A series of at least 9 different experiments were performed to measure the retention of hexachlorophene in the stratum corneum or horny layer. The experiments involved the application of hexachlorophene from suspensions and solutions of hexachlorophene in "pHisoHex" (a suspension of 3% hexachlorophene produced by Wintrhop Laboratories, N.Y., N.Y.), DMA and DEA to the forearms, palms and backs of hands. The preparations were allowed to remain in contact with the skin for periods of time, varying from 15 seconds to as long as 20 minutes before the area was washed. Measurements were conducted at specified intervals of time and the areas were washed with soap and

water in a consistent fashion for each of the comparisons that were made. In every comparison the preparations applied which were in accordance with the invention showed enhanced retention over the corresponding preparation which did not utilize the amides of this invention. The lowest degree of enhancement achieved was about a 5-fold increase in retention while enhanced results showing as high as about a 110-fold increase in retention were observed. Similar results have been shown for trichlorosalicylanilide. Iodine when applied in a composition according to the invention also shows increased retention and therefore exhibits the beneficial effects discussed above. The same is true of special anti-acne and antiseborreic preparations particularly those containing sulfur as the major pharmaceutically active compound. Sulfur gives increased retention when present in a composition according to the invention and therefore greater and longer lasting concentrations of this substance can be maintained in the affected areas of the skin.

Emollient preparations in accordance with the invention, such as for example, lanolin and lanolin alcohols and their ethoxylated and/or acetylated products; glycerol, glycols and their derivatives; fatty acids, their esters, their alcohols and their derivatives, show increased percutaneous absorption and increased retention resulting in improved softening and moisturizing effects.

Sex hormones also show increased percutaneous absorption and retention when applied in accordance with the invention. Androgens, estrogens and progestogens are examples of such hormones. Testosterone has recently been shown to stimulate the growth of scalp hair. Thus increasing the amount of testosterone which penetrates to the hair follicle root and maintaining its reservoir there will further increase hair follicle activity.

Estrogens have long been used in a wide variety of beautifying preparations. Thus the invention makes possible the percutaneous absorption and retention of larger quantities of these beautifying chemical compounds.

It has also been found that the retention of sunscreens can be increased when incorporated in preparations in accordance with the invention. The utility of this invention for application of sunscreens is immediately obvious since it is now possible for the sunscreen to be retained in the horny layer of the skin for long periods of time despite frequent bathing, sweating or rubbing of clothing over the area to be protected from the harmful rays of the sun. Some examples of such sunscreens are para-aminobenzoic acid, amyl p-dimethylaminobenzoate, salicylic acid, cinnamic acid and benzophenones and their derivatives.

Various products of crude coal tar which are used in the treatment of eczema, psoriasis and seborrheic dermatitis, such as "BALNETAR", an extract of crude coal tar and "SEBUTONE", a cleanser product containing sulfur, salicylic acid, hexachlorophene and crude coal tar extract both, produced by the Foster-Milburn Company, have been applied in preparations in accordance with the invention have been shown to have enhanced retention in the horny layer.

The beneficial photodynamic action of various chemical substances such as various derivatives, extracts components and products of crude coal tar for example in treatment of psoriasis by the Goeckerman regimen or its modifications, is also enhanced when such substances are applied in compositions in accordance with the invention.

Another outstanding application of the present invention is in patch testing. This is one of the most widely used and simplest of methods for testing the skin to determine and identify sensitization and/or irritation potential to various substances. It is particularly useful in eruptions of contact dermatitis (dermatitis venenata) caused by plants, industrial chemicals, medicines, cosmetics, food and household articles.

The patch test consists of the application to uninjured skin, contiguous to the involved area, of substances suspected to be causes of the sensitivity and/or the irritation reaction. This is done by saturating a small piece of gauze with one of these substances in a concentration that will not cause irritation in the average person. It is covered by a piece of impermeable protective material such as cellophane and then applied to the skin by adhesive plaster. Ready-made patches are available. The patches are usually allowed to remain in place forty-eight hours (unless there is pronounced irritation). It may be two or three days later before a positive reaction shows, so it is important to watch for delayed reactions.

There are many drawbacks in this method of testing. For example, the gauze and the tape holding it must remain in place for a protracted period. This is uncomfortable and inconvenient. There may even be a reaction of the tape.

Using the compositions of this invention, a suspected chemical may be applied to the skin, left untouched for about five minutes and the subject allowed to go on his way without gauze pads. He may even bathe normally and put clothing over the area of application.

Thus a process is provided by which suspected substances such as poison ivy, potassium dichromate, phenylene diamine, azo dyes, various antioxidants, epoxy resins

Thus it can be seen that antibiotic activity was retained consistently longer when the germicide or antibiotic was applied according to the present process.

Chloromycetin and oleandomycin were also retained well when applied in DMA and maintained good bacterial antibiotic activity in the horny layer for over 24 hours after a 10 minute application followed by a washing.

Preparations of 0.01—0.02 cc. of 2% tetracycline in pure DMA, and distilled water were applied to whole skin samples in vitro and incubated at about 37°C.; at about 50% relative humidity for 20 hours. The epidermis was carefully removed and punch biopsies were taken. These punch biopsies were implanted on blood agar plates innoculated with *alpha streptococcus* and *staphylococcus albus* both of which were sensitive to tetracycline by the disc method. Many such experiments were done. About 50% of the time, the skin treated with DMA and tetracycline would show some inhibition of growth. The water and tetracycline failed to show inhibition at any time. Erythromycin, dimethylchlortetracycline, iodochlorhydroquin and chloramphenicol all show enhanced activity when applied in accordance with the instant process.

Despite attempts to insure complete uniformity it must be recognized and understood that the exact qualities and characteristics of skin vary somewhat from subject to subject. Therefore, it may be impossible to exactly duplicate the quantitative results achieved in some of the above experiments. However, given similar samples of skin the same ratios of percutaneous absorption and retention should be observed between the various preparations applied in accordance with the teachings of the specification.

The most preferred amide for utilization in the compositions of the invention is N,N-dimethylacetamide (DMA), a liquid of the formula $CH_3CO.N(CH_3)_2$, having a boiling point of 165.5°C. and a specific gravity of 0.943. It is miscible with water and fixed oils in all proportions. This substance has been shown by the prior art to be completely acceptable for topical or parenteral application. At high concentrations some subjects have experienced transient erythema (very slightly burning sensation) for 4—5 minutes after application of preparations containing very high levels of DMA. However, no lasting effects or discomfort were noted.

N,N-dimethylformamide (DMF) is also a preferred amide for use in the compositions of the invention. However, due to its relatively higher toxicity which has been reported for experimental animals, this substance should be studied regarding human toxicity and used with caution.

The amides used in the compositions of this invention may be used alone, in combination with the stable, topically active compounds or with other additional pharmaceutically acceptable surface active agents, emulsifiers, solvents, vehicles or other pharmaceutically acceptable bases. For example, the amides are compatible in all proportions with the following solvents or vehicles; water, isopropanol, ethanol and fatty acid esters to name a few widely used solvents.

It has been shown that the relationship between percutaneous absorption and retention for any given compound and the percentage of amide in the preparation is approximately directly proportional, i.e., the more amide utilized the greater the degree of percutaneous absorption and retention. Thus the only limitations upon the ratio of components in any given preparation are dictated by practical considerations.

One can, of course, use preparations containing 100% amide. However, since there is a certain leveling effect at the upper concentration of amide used and since one should have an appreciable amount of stable, topically active chemical component present for treatment purposes, it can be said that it is preferable to utilize from 25% to 95% amide in the composition and process of this invention. Due to the enhanced rates of absorption and retention preparations containing as much as about 99.999% amide and only 0.001% stable, topically active compounds can be applied with beneficial results.

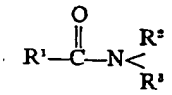
The effect of the present invention upon the rate of percutaneous absorption or retention takes place almost immediately upon application of the preparation to the skin. Thus it can be said that any contact with the skin utilizing the compositions of the invention shows enhanced results over contact for the same period of time by the chemical compound alone or in compositions not utilizing the amides which are present in the compositions of the invention.

Application of the stable, topically active chemical compound to the skin in a composition in accordance with the instant invention for a period of about five minutes gives the optimum retention in relation to the length of contacting time. Longer contacting periods while giving somewhat greater total retention concentration or more percutaneously absorbed substance are insignificant in relation to the total amount absorbed or retained within the optimum time period of about 5 minutes.

WHAT WE CLAIM IS:—

1. A process for producing a composi-

tion to be applied to the skin and having increased percutaneous absorption through and retention in skin as hereinbefore defined which comprises solubilizing a stable, topically active beneficial chemical compound as hereinbefore defined in a pharmaceutically acceptable vehicle having as one component an amide having the structural formula:

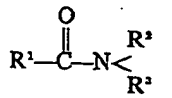


wherein R^1 is a hydrogen or methyl radical, R^2 is a hydrogen or alkyl radical containing not more than 2 carbon atoms; and R^3 is an alkyl radical containing not more than 2 carbon atoms.

2. A process according to claim 1, in which the amide is N,N-dimethyl acetamide; N,N-dimethyl formamide or N,N-diethyl acetamide.

3. A process according to any one of the preceding claims, in which from 0.001% by weight to 80% by weight of the stable, topically active beneficial chemical compound is solubilized in from 99.999% by weight to 20% by weight of the pharmaceutically acceptable vehicle.

4. A composition to be applied to the skin and having increased percutaneous absorption through and retention in skin comprising a stable, topically active chemical compound which is an anti-acne agent, an anti-inflammatory agent, an anticholinergic, an emollient, a sex hormone, crude coal tar, an antipsoriatic agent or an antimetabolite, solubilized in a pharmaceutically acceptable vehicle having as one component an amide having the structural formula:



wherein R^1 is a hydrogen or methyl radical, R^2 is a hydrogen or alkyl radical containing not more than 2 carbon atoms; and R^3 is an alkyl radical containing not more than 2 carbon atoms.

5. A composition according to claim 4 in which the topically active chemical compound is anthracene.

6. A composition according to claim 4 in which the topically active chemical compound is sulfur.

7. A composition according to claim 4 in which the topically active chemical compound is glycerol.

8. A composition according to claim 4 in which the topically active chemical compound is testosterone.

9. A process for producing a composition to be applied to the skin according to claim 1 substantially as hereinbefore described with reference to the Examples.

10. A composition to be applied to the skin according to claim 4 substantially as hereinbefore described with reference to the Examples.

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